REMARKS

1. Preliminary Remarks

a. Status of Claims

Claims 25, 26, 29, 30, and 35-38 are pending and under active consideration. Claims 35-38 are amended. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of this application. Upon entry of the amendments, claims 25, 26, 29, 30, and 35-38 will be pending and under active consideration.

b. Amendment to the Claims

Claims 35-38 have been amended and are now directed to a vector comprising a heterologous sequence, wherein the heterologous sequence consists of the sequence of the nucleic acid of claims 25, 26, 29, or 30. Support for amended claims 35-38 can be found throughout the specification, for example, paragraph 0027. One of ordinary skill in the art would recognize that features other than the heterologous sequence would be necessary for a functional vector.

c. Declaration/Oath

On page 2 of the Office Action, the Examiner objected to the declaration filed May 14, 2004 because the inventor signatures and relevant information corresponding to their signatures is illegible. Applicant hereby submits a newly executed oath/declaration by the inventors Itzhak Bentwich and Amir Avniel. Accordingly, Applicant respectfully submits that the objection is now moot and should be withdrawn.

d. Priority

On pages 3 and 4 of the Office Action, the Examiner objects to the priority claim for being confusing between the Application Data Sheet filed May 14, 2004 and the cross reference section of the instant application. In response, Applicant hereby submits a Supplemental Application Data Sheet according to 37 C.F.R.§1.76(c) with this response showing the relationship of the priority applications to the instant application. This newly submitted Supplemental Application Data Sheet constitutes the specific reference required by 35 U.S.C. §§119(e) or 120, and 37 C.F.R.§§1.78(a)(2) or (a)(5), and need not otherwise be made part of the specification.

2. Patentability Remarks

a. 35 U.S.C. §101

On pages 4-16 of the Office Action, the Examiner rejects the claims 25, 26, 29, 30, and 35-38 under 35 U.S.C. §101, for allegedly lacking utility. In order to satisfy the utility requirement, a specific and substantial utility must either (i) be cited in the specification or (ii) be recognized as well as

established in the art, and the utility must be credible. *See In re Fisher* 421 F.3d 1365, 1371 (2006) and *Revised Interim Utility Guideline Training Materials* ("Guidelines").

(1) Specific Utility

A specific utility is a utility that is specific to the particular claimed subject matter, which is in contrast to a general utility that would be applicable to a broad class of inventions. *See In re Fisher* 421 F.3d at 1371 and Guidelines. Applicant respectfully submits that the application provides a specific utility for the claimed microRNA-related nucleic acids in accordance with *In re Fisher* and the Guidelines.

In *Fisher*, the claims at issue were directed to five (5) out of more than 32,000 EST that were disclosed in the application. Each of disclosed ESTs was from a cDNA library from pooled leaf tissue of a maize plant. The Fisher application did not disclose the location of the ESTs in the genome or the function of the underlying genes. Fisher asserted that the utilities for claimed ESTs were (1) serving as a molecular marker; (2) measuring the level of mRNA in a tissue sample; (3) provide a source of primers for PCR of specific genes; (4) identifying the presence or absence of a polymorphism; (5) isolating promoters via chromosome walking; (6) controlling protein expression; and (7) locating genetic molecules of other plants and organisms. *See Id.* at 1367 and 1368. It is important to note that each of the utilities asserted were not limited to any specific gene, genetic location or protein.

The *Fisher* court concluded that the asserted utilities were clearly not "specific." The court explained that any EST transcribed from any gene in maize could perform the seven uses such as being a molecular marker, a primer, or measure the level of RNA in a tissue sample. In other words, nothing about the seven alleged uses separated the claimed ESTs from the vast number of other ESTs also disclosed in the application. The keystone to the lack of specific utility in *Fisher* is that the claimed ESTs **did not correlate to an underlying gene of known function found in the maize genome**.

Similar to *Fisher*, the current application discloses a large number of nucleic acid sequences. In stark contrast to *Fisher*, however, the instant application provides that each of the disclosed nucleic acids maybe used to target and modulate expression of **specific** gene transcripts. Table 7, lines 146,394-146,403 and lines 146,416-146,422 and Table 8, lines 435,535-435,555 of the specification disclose that the **claimed microRNA-related sequences specifically target** mRNA transcripts of the Epidermal Growth Factor Receptor (EGFR) gene. Consequently, the claimed nucleic acids are of a **specific and unique nature** because these nucleic acids regulate the translation of mRNAs from the **specific target gene EGFR**. Accordingly, the asserted utility of the claimed invention is not vague or meaningless, and there is a well-defined public benefit to regulating the EGFR gene.

(2) Substantial Utility

To satisfy the "substantial" utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public. *See In re Fisher* at 1371 and the Guidelines. Applicant respectfully submits that the application provides a substantial utility for the claimed microRNA-related nucleic acids in accordance with *In re Fisher* and the Guidelines.

In Fisher, it was admitted that the underlying genes for the ESTs had no known function. Fisher argued this was irrelevant because the seven asserted uses (discussed above) were not related to the function of the underlying genes. Importantly, Fisher failed to provide any evidence that any of the claimed ESTs could be used for any of the asserted uses. Consequently, the *Fisher* court concluded that the claimed ESTs were "mere 'objects of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *See Id.* at 1373 quoting *Brenner v. Manson*, 383 U.S. 519 (1966).

In further sharp contrast to *Fisher*, the present application discloses that the claimed nucleic acids may be used to bind and regulate mRNA transcripts of EGFR. *See* Table 7, lines 146,394-146,403 and lines 146,416-146,422. At the time of filing, it was known in the art that the function of EGFR was involved in the control of cell growth and differentiation as well as associated with human eye diseases. *See* Thaung *et al., Human Molecular Genetics* 11:755-767 (2002), Table 8, lines 435,535-435,555, and Table 9, line 38060. Thaung demonstrates that EGFR mutation in mice results in open eyelids and curly whiskers exposing the eyes to environmental damage such as infection or dust. Applicant further submits that EGFR was also expressed in retinoblastoma cells and may be target for anti-EGFR therapy. *See* abstract of Bosch *et al., Graefes Arch Clin. Exp. Opthalmol.* 243:156-162 (2005). In addition, Applicant submits that SEQ ID NO: 6821380 (hairpin) related miRNA nucleic acids are expressed in human retinoblastoma and play significant roles in regulating tumor genesis. *See* Zhao *et al., Childs Nerv. System* , DOI 10.1007/s00381-008-0701-x (2008).

The evidence described above clearly supports that the claimed nucleic acids have a number of presently available benefit to the public, including: (1) as a diagnostic of retinoblastomas cells; (2) modulating expression of EGFR in retinal cells; and (3) maintaining homeostasis in retinal cells by targeting EGFR. In view of the application providing particular targets of known function for the claimed microRNA-related nucleic acids, Applicant respectfully submits that the specific and substantial utility requires are satisfied in accordance of Fisher and the Guidelines.

(3) Credible Utility

An asserted utility is credible if the assertion is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided. An assertion is credible unless (i) the logic underlying the assertion is seriously flawed, or (ii) the facts upon which the assertion is based are

inconsistent with the logic underlying the assertion. Accordingly, the invention must be operable to achieve useful results. *See Guidelines* at page 5 and *In re Swartz*, 232 F.3d 862 (Fed. Cir. 2000). The evidentiary standard that the Patent Office **should** use throughout *ex parte* examination in setting forth the utility rejection is preponderance of the totality of the evidence under consideration. A preponderance of the evidence exists when it suggests that it is more likely than not that the assertion is true. *See Herman v. Huddleston*, 459 U.S. 375 (1983). To overcome the presumption of truth of the Applicant's assertion of utility, the Examiner must establish by presenting countervailing facts that it is more likely than not that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility.

At page 14 of the Office Action, the Examiner asserts that a credible utility is lacking because the claimed polynucleotides have not been experimentally verified and there is no experimental evidence of even a single biological function. The Examiner further states the function is asserted solely on the basis of a computer program designed to predict miRNA-like hairpin sequences and mature miRNAs derived thereofrom. The Examiner further asserts that the answer lies in the predictive quality of the program used to identify the miRNAs and their target sites. The Examiner points out on page 9 of the Office Action that miRNA prediction algorithms used in the art have a false positive rate of between 22% and 39% citing Bentwich *et al., FEBS Lett.* 579:5904-5910 (2005) ("Bentwich") and Martin *et al., J. Biosci.* 32:1049-1052 (2007) ("Martin"). Applicant respectfully disagrees.

Applicant respectfully submits that the Examiner has not considered the asserted utility as discussed above for using the claimed polynucleotides for modulating expression of specific mRNA targets. Whether or not the claimed polynucleotides actually exist in a biological system, and whether the true biological function of any predicted miRNA sequence has been validated according to Krutzfeldt (cited by Examiner on pages 9 of the Office Action) are irrelevant. The proper inquiry is instead whether a person of ordinary skill in the art would believe that the claimed polynucleotides **may be** used to modulate expression of the specific mRNA targets.

Paragraph 0357 of the application discloses that the mRNA targets of the claimed polynucleotides were identified as being consistent with the free energy and spatial structure of target binding sites of known miRNAs. The method as described in paragraph 0357 for identifying target binding sites of miRs is based upon studies at the time of filing demonstrating that miRs bind to target binding sites as disclosed in references such as Wightman *et al.* (1993), Reinhart *et al.* (2000), Slack *et al.* (2000), Lau *et al.* (2001), Lagos-Quintana *et al.* (2001), and Moss *et al.* (1997), which are all cited in the Information Disclosure Statement filed herewith.

The Examiner's rejection for lack of credible utility is presented despite the fact that Applicant's algorithm does not violate any scientific principle and is wholly consistent with contemporary knowledge regarding miRNA prediction algorithms and the Examiner's cited algorithm from Bentwich and Martin.

The algorithms acknowledged by the Examiner predict miRNA/target binding predict at a 61-78% success rate. Yet, the Examiner impermissibly requires that Applicant provide absolute certainty (100%) that miRNA sequences related to hairpin precursor SEQ ID NO: 6821380 such as miRNA SEQ ID NO: 159 functions as a miRNA and targets/modulates EGFR.

The Examiner has also provided no evidence to countervail that the microRNA SEQ ID NO: 159 is likely to inhibit expression of the EGFR protein. The Applicant submits that the Examiner has failed to present the required countervailing facts that it is more likely than not that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility. In other words, the Examiner has failed to provide greater than 50% assurance that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility. Accordingly, the Examiner has failed to provide by a preponderance of the evidence that Applicant's asserted utility fails. In view of the foregoing, Applicant asserts that the claimed nucleic acids have specific, substantial and credible utility, and requests that the rejection of claims 25, 26, 29, 30, and 35-38 under 35 U.S.C. §101 for lacking utility has been overcome and therefore should be withdrawn.

b. 35 U.S.C. §112, First Paragraph (Enablement)

On page 16 of the Office Action, the Examiner rejected claims 25, 26, 29, 30, and 35-38 under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the enablement requirement. The Examiner asserts that there is no support in the instant application for the claimed nucleic acids functioning as miRNAs, and that the claimed nucleic acids lack utility. Applicant respectfully disagrees.

As discussed above, the claimed nucleic acids have a credible, substantial and specific utility, namely in modulating expression of the EGFR transcript, which in turn, may respectfully alter retinal cell development and differentiation. Moreover, Table 7, lines 146,394-146,403 and lines 146,416-146,422 and Table 8, lines 435,535-435,555 of the specification first disclosed this asserted utility of the claimed nucleic acids to inhibit EGFR. Therefore, the Applicant submits that the function of the claimed nucleic acids was known at the time of filing. In view of the foregoing remarks Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 25, 26, 29, 30, and 35-38 under 35 U.S.C. §112, first paragraph.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification of to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

POLSINELLI SHUGHART PC

Dated: March 10, 2009

On behalf of: Teddy C. Scott, Jr., Ph.D.
Registration No. 53,573

By: /Paul A. Jenny/
Paul A. Jenny
Registration No. 59014
Customer No. 37808

POLSINELLI SHUGHART PC
180 N. Stetson Ave., Suite 4525
Chicago, IL 60601
312.819.1900 (main)
312.602.3955 (E-fax)
312.873.3613 (direct)